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内容:中等症～重症の潰瘍性大腸炎には抗腫瘍壊死因子様サイトカイン 1A(TL1A)モノクローナル抗体 tulisokibart が有望

出典:Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulisokibart for Ulcerative Colitis. The New England journal of medicine. 2024 Sep 26;391(12);1119-1129

https://pubmed.ncbi.nlm.nih.gov/39321363/

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大腸の粘膜に炎症が起こることにより下痢や腹痛、血便(便に血が混ざる)などの症状が現れる原因不明の潰瘍性大腸炎(UC)の治療は、生物学的生物学的製剤や低分子化合物の出現により大きく変化している。中等症～重症の潰瘍性大腸炎の治療において、抗腫瘍壊死因子様サイトカイン 1A(TL1A)モノクローナル抗体 tulisokibart の効果を、米国・マウントサイナイ医科大学の研究者らは「ARTEMIS-UC 試験」で示した。研究の成果は、NEJM 誌 2024 年 9 月 26 日号で報告された。

14ヵ国の施設で実施した二重盲検無作為化プラセボ対照第II相試験であり、2021 年 7 月～2022 年 10 月に参加者を登録、tulisokibart(1 日目に 1,000mg、2 週・6 週・10 週目に 500mg)を静脈内投与する群、またはプラセボ群に無作為に割り付けた。コホート 1 には、効果の可能性を評価する遺伝子診断検査の結果を問わずに患者を登録し、コホート 2 には、同検査で効果の可能性があると判定された患者だけを登録した。主解析はコホート 1 で行い、主要エンドポイントは 12 週の時点での臨床的寛解とした。コホート 1 に 135 例を登録し、tulisokibart 群に 68 例(平均[±SD]年齢 40.4[±14.4]歳、女性 34 例[50%])、プラセボ群に 67 例(42.2[±16.3]歳、29 例[43%])を割り付けた。12 週時の臨床的寛解の達成率は、プラセボ群が 1%であったのに対し、tulisokibart 群は 26%と有意に優れた(群間差:25%ポイント、95%信頼区間[CI]:14～37、p＜0.001)。また、内視鏡的改善や組織学的改善などのすべての副次エンドポイントに関して、一貫した有効性が示された。一方、効果の可能性があると判定された患者は 2 つのコホートを合わせて 75 例で、tulisokibart 群が 38 例(平均[±SD]年齢 37.3[±15.7]歳、女性 20 例[53%])、プラセボ群は 37 例(同 38.6[±13.0]歳、13 例[35%])で、その臨床的寛解の達成率は、プラセボ群が 11%であったのに比べ、tulisokibart 群は 32%であり有意に良好だった(群間差:21%ポイント、95%CI:2～38、p＝0.02)。コホート 1 と 2 を合わせた患者集団における有害事象は、tulisokibart 群で 46%、プラセボ群で 43%に発現した。重篤な有害事象は、それぞれ 1 例(1%)および 7 例(8%)に認めた。

これらの知見を総合的にみると、TL1A の遮断は、中等症～重症の活動期潰瘍性大腸炎における新たな作用機序であり、先進治療歴の有無にかかわらず有効であることを示すエビデンスとなる。

The NEW ENGLAND JOURNAL of MEDICINE

Phase 2 Trial of Tulisokibart for Ulcerative Colitis

A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: Phase 2 Trial of Anti-TL1A Monoclonal Antibody Tulisokibart for Ulcerative Colitis by B.E. Sands et al. (published September 28, 2024)

In this trial, researchers evaluated the efficacy and safety of tulisokibart, a tumor necrosis factor–like cytokine 1A (TL1A) monoclonal antibody, in patients with moderately to severely active ulcerative colitis.

Ulcerative colitis is a chronic, inflammatory gastrointestinal disorder with symptoms that include abdominal cramping, diarrhea, and rectal bleeding.

WHY WAS THE TRIAL DONE?

Available biologic and small-molecule therapies for ulcerative colitis often do not induce clinical remission among patients who have not had a response to conventional or advanced therapies. New approaches are needed. A genetic-based diagnostic test was designed to identify patients with an increased likelihood of response to an anti-TL1A antibody.

HOW WAS THE TRIAL CONDUCTED?

The patients were divided into two cohorts. In cohort 1, patients who were enrolled regardless of their likelihood of response were assigned to receive intravenous tulisokibart (1000 mg on day 1 and 500 mg at weeks 2, 6, and 10) or placebo. In cohort 2, only patients with a positive test for likelihood of response were enrolled and underwent randomization. The primary analysis, performed in cohort 1, assessed clinical remission at week 12. In addition, patients with a positive test for likelihood of response from cohorts 1 and 2 were combined in prespecified analyses to assess the efficacy of tulisokibart in this subpopulation.

WHO: 135 adults in cohort 1 and 40 adults in cohort 2

CLINICAL STATUS: Diagnosis of moderately to severely active ulcerative colitis

Glucocorticoid dependence or failure of conventional or advanced therapies for ulcerative colitis

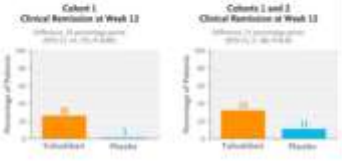
TRIAL DESIGN

RESULTS

In cohort 1, a higher percentage of patients had clinical remission at week 12 with tulisokibart than with placebo.

Among patients from cohorts 1 and 2 with a positive test for likelihood of response, a higher percentage of patients had clinical remission with tulisokibart than with placebo.

Among all enrolled patients (cohorts 1 and 2), the incidence of adverse events was similar in the tulisokibart and placebo groups. Most adverse events were mild to moderate in severity.



CLINICAL REMISSION

Clinical remission was defined by a modified Mayo score consisting of three components (each on a scale from 0 to 3, with higher scores indicating greater severity): a rectal bleeding subscore of 0, a stool frequency subscore of 0 or 1, and an endoscopic subscore of 0 or 1.

LIMITATIONS AND REMAINING QUESTIONS

- This phase 2 trial could not adequately evaluate the therapeutic index of tulisokibart. Assessment of larger numbers of patients over longer periods of time will provide more precise efficacy and safety evaluations.
- Efficacy among patients with a positive test for likelihood of response was based on pooled patients from cohorts 1 and 2. The analysis is therefore limited by the small sample size and may be susceptible to selection bias due to differences between the cohorts.

CONCLUSIONS

In this 12-week trial, treatment with tulisokibart, an anti-TL1A monoclonal antibody, was more effective than placebo for inducing clinical remission in patients with moderately to severely active ulcerative colitis.

LINKS: FULL ARTICLE | NEJM QUICK TAKE

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT04982757

Trial funding: Prometheus Biosciences, a subsidiary of Merck

Full citation: Sands BE, Feagan BG, Peyrin-Biroulet L, et al. Phase 2 trial of anti-TL1A monoclonal antibody tulisokibart for ulcerative colitis. N Engl J Med 2024;391:1124-28. DOI: 10.1056/NEJMoa2314678